The relationship between white matter microstructure and general cognitive ability in patients with schizophrenia and healthy participants in the ENIGMA Consortium

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Abstract

Objective: Schizophrenia has recently been associated with widespread white matter microstructural abnormalities, but the functional effects of these abnormalities remain unclear. Widespread heterogeneity of results from studies published to date preclude any definitive characterization of the relationship between white matter and cognitive performance in schizophrenia. Given the relevance of deficits in cognitive function to predicting social and functional outcomes in schizophrenia, we carried out a meta-analysis of available data through the ENIGMA Consortium, using a common analysis pipeline, to elucidate the relationship between white matter microstructure and a measure of general cognitive performance, intelligence quotient (IQ), in patients with schizophrenia and healthy participants.

Methods: Our meta-analysis, the largest of its kind to date, included 760 patients with schizophrenia and 957 healthy participants from 11 participating ENIGMA-Consortium sites. For each site, principal component analysis was used to calculate both a global fractional anisotropy component (gFA), and a fractional anisotropy component for six long association tracts (LA-gFA) previously associated with cognition.

Results: Meta-analyses of regression results indicate that gFA accounted for a significant amount of variation in cognition in the full sample (effect size, ES=0.27 CI=0.17-0.36), with similar effects sizes observed for both patient (ES=0.20, CI=0.05-0.35) and healthy participant subgroups (ES=0.32, CI=0.18-0.45). Comparable patterns of association were also observed between LA-gFA and cognition for the full sample (ES=0.28, CI=0.18-0.37), patient (ES=0.23, CI=0.09-0.38), and healthy participant subgroups (ES=0.31, CI=0.18-0.44).

Conclusions: This study provides robust evidence that cognitive ability is associated with global structural connectivity, with higher fractional anisotropy associated with higher IQ. This association was independent of diagnosis; while patients tended to have lower FA and lower IQ than controls, the comparable size of effect in each group suggested a more general, rather than disease-specific, pattern of association.

Introduction

Schizophrenia is a leading cause of disability worldwide (1). Although this disability is typically characterised by clinical symptom severity, the cognitive deficits associated with the disorder strongly predict social and functional outcomes (2-4). These deficits are observed across multiple cognitive domains (5), suggesting that broad, rather than regionally specific, changes in brain function are likely to underpin these deficits.

At a neural systems level, robust evidence of widespread differences in both white and gray matter has been demonstrated in large samples of patients with schizophrenia versus healthy participants (6, 7). Compared to healthy participants, people with schizophrenia show widespread thinning of cortical gray matter, and reduced cortical surface area, particularly in frontal and temporal lobe regions (7). Analysis of subcortical gray matter volumes similarly showed evidence of widespread differences, including bilateral volume abnormalities of the hippocampus, amygdala and thalamus (8). Recently, in the largest diffusion tensor imaging study of white matter abnormalities undertaken to date, widespread reductions in fractional anisotropy (FA) were observed for a majority (19/25) of tracts, with largest effects observed for global white matter FA, and more locally, in large tracts including the anterior *corona radiata* and corpus callosum (6).

Taken collectively, these widespread abnormalities indicate a disease pathology reflective of generalised changes to the brains structural network and functions. This is consistent with the disconnectivity hypothesis of schizophrenia (9, 10), which suggests that functional impairments and disability results from abnormal and inefficient communication among distributed networks of brain regions (11, 12). This hypothesis would be further supported if these indices of disconnectivity could be directly related to variation in cognitive performance and functional outcomes, but well-powered studies in this area are currently lacking.

To address this gap, here we aimed to examine the relationship between brain structure and cognitive function on a large, global scale. To do this, we carried out a meta-analysis of available data through the ENIGMA Consortium, using a common analysis pipeline, to elucidate the relationship between white matter microstructure and a measure of general cognitive performance, intelligence quotient (IQ), in patients with schizophrenia and healthy participants. We hypothesized that 1) a significant positive correlation would be observed between white matter microstructure and IQ across samples, and 2) this association would be moderated by diagnosis.

Methods

META-ANALYSIS

Study Sample

Data for the current study was collected via the ENIGMA-Schizophrenia DTI working group and consisted of a sub-sample of participating sites in *Kelly et al* (6). Inclusion criteria for this current study was based on the availability of data processed using the ENIGMA DTI protocol, and measures of estimated IQ for each participant in a given dataset. The final sample consisted of 11 sites with both DTI and IQ, totalling 957 controls and 760 patients (detailed demographics in table 1). Each study sample had been assessed with participant's written informed consent approved by local Institutional Review Boards. Individuals with bad-quality diffusion images were excluded from the analysis.

Measurement of IQ

IQ was calculated for healthy controls and patients with a confirmed diagnosis of schizophrenia. IQ The Wechsler Scale of Adult Intelligence (WAIS) was used to estimate IQ in all 11 studies. Ten sites calculated IQ based on the English version of the test (WAIS, 3rd edition); at the Madrid site, the Spanish version of the WAIS was used. The WAIS consists of a battery of verbal and non-verbal subtests, scores of which are combined to derive a verbal IQ, performance IQ and full-scale (total) IQ score. Because not all sites had both verbal and performance score, our analyses were based exclusively on full-scale IQ scores. The number of subtests used to determine this full-scale score also varied between sites. Following previous large-scale multi-site analysis of IQ in schizophrenia by other consortia (e.g. COGENT) (13) IQ scores calculated for all sites were based on pro-rated subtest scores. For 9 of the 11 sites this was based on three or more subtests. At two sites IQ was calculated based on only two subtests being available for these samples (ASRB & MPRC).

Image Acquisition and Processing

Image data was acquired using site specific diffusion MRI sequences. Details of study type, scanner and acquisition parameters for each site are presented in supplementary table 1. For each site, preprocessing, including eddy current correction, echo-planar imaging-induced distortion correction, and tensor fitting, was carried out locally based on local protocols and procedures, and further informed by quality control pipelines available as part of the ENIGMA-DTI webpage (http://enigma.ini.usc.edu/protocols/dti-protocols) and NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse). To correct for subject motion during image acquisition, preprocessing included the alignment of diffusion weighted images to the b=0 using linear image registration.

Individual subject data with excessive motion was not included in this analysis. As per Kelly *et al.* (6), harmonization of preprocessing schemes was not enforced across sites to allow individual sites to use existing pipelines that may be more appropriate for their data acquisition. Following preprocessing, harmonized image analysis of DTI measure of FA was then conducted at each site in exactly the same manner using the ENIGMA-DTI protocol http://enigma.ini.usc.edu/protocols/dti-protocols/). The ENIGMA-DTI protocol using TBSS (14) outputs averaged FA across all white matter tracts (listed in supplementary table 2). The TBSS output includes FA values for both right and left bilateral white matter tracts, and an average FA value based on the average FA from both hemispheres. Average FA values were used in for this analysis to minimize multiple comparisons and any potential issues of site-based left/right flipping which would limit interpretations of a lateralized analyses.

Statistical Analysis

Per-Site Analysis

Calculation of FA is based on specific acquisition protocols including scanner make and model, diffusion sequence parameters, methods of tensor estimation models, and processing pipelines (15, 16). To overcome this systematic limitation, preliminary analysis was carried out individually at each site to assess the association between white matter tract microstructure and estimates of IQ. Only then were summary statistics compared, thus removing the issue of variances across sites due to scanner or acquisition parameters.

Per-Site Latent Fractional Anisotropy Factor Analysis

To reduce the burden of multiple testing, we undertook principal components analysis of white matter tracts indexed by diffusion tensor imaging to index white matter. For each site separately, principal components analysis, implemented in SPSS, was used to derive an un-rotated first principal component, representing global white matter, termed 'gFA'. In addition, six long association tracts, which have been previously associated with variation in IQ (see supplementary table 2), were also subjected to a principal components analysis, for which the first un-rotated principal component was again derived and termed 'LA-gFA'. Calculation of these components followed a similar approach to analyses carried out by Cox et al(17) and Penke et al(18). These studies reported that a latent factor explained a substantial portion of the variance in FA across all white matter tracts, whereby at an individual level, higher FA in a single tract predicted higher FA in all tracts. Generation of a single principal component for our analyses was designed to minimize the need to control for multiple comparisons across all white matter tracts. For each PCA, we examined scree plots and the

extraction values to determine if tract FA values could be represented by a single latent factor. Comparable scree plots were observed for data across all sites for gFA, figure 1a. The loadings of each white matter tract on the first principal component are presented in supplementary data 2. FA variance explained by the first un-rotated component ranged from 44-70%, with a median of 56% (see supplementary table 3). Our second PCA analysis included FA of six long association tracts (LA-gFA) based on white matter tracts previously associated with IQ in the literature (19-26). The six tracts included: the arcuate fasciculus, anterior limb of the internal capsule, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and the cingulate bundle. Like gFA, comparable scree plots were observed for data across all sites for LAgFA, figure 1b.

The same PCA method was used to derive both global and long association latent factors for sites that included secondary diffusion parameters. Secondary parameters included mean diffusivity, radial diffusivity, and axial diffusivity.

Per-Site Assessing the variance in IQ explained by white matter microstructure

To calculate the variance in IQ explained by white matter microstructure, a hierarchical regression analysis was carried out on a site-by-site basis (using SPSS-24). After controlling for age and gender, the r-squared change was used to estimate the variance in IQ explained by either gFA or LA-gFA on IQ. These regression analyses were carried out for both the full sample, and for patients and controls separately, to allow determination of the effects of diagnosis.

Meta-Analysis

Comprehensive Meta-Analysis (https://www.meta-analysis.com/) software (statistical consultancy was not provided) was used locally to analyse summary data from all 11 contributing sites. The meta-analysis consisted of a two-level model, 1) a random effects model estimating the average effect size by combining the observed effect sizes across all studies in the sample; and 2) a mixed effects model incorporated diagnosis as a moderator variable to estimate the between-group variation and determine the effect of diagnosis on the observed association between white matter micorstructure and IQ. Secondary analysis was carried out to determine the moderating effects of gender on the association between white matter tracts and IQ.

Results

Meta-Analysis

Demographic & clinical information for the total ENIGMA samples of 957 healthy controls and 760 patients with schizophrenia are presented in table 1. The mean age for patient and control samples across all sites was 36 (SD=9.1 and 10.1 respectively). With adolescent sites removed, the mean age for patient and control samples was 39 (SD=5.55 and 5.98 respectively). The patients were 70% male (males=535, females=225), a higher ratio compared to the control group (56% male; males=539, females=418), $X^2(1)=4.2$, $p=0.04$. The mean IQ across patient samples was 97 (SD=16.47) and 113 (SD=13.14) for healthy participants; see table 1. These values are somewhat higher than might be expected, especially for the patient group; a review of table 1 suggests that this difference is due to the IQ of patients in the ASRB dataset, which was the only dataset to have a mean patient IQ >100.

Analysis of mean and standard deviation IQ across sites shows that on average, patients had significantly lower IQ compared to healthy controls (mean IQ HC=113 sd=5.82, Sz=97 sd=8.24, t(27)=5.94, $p<0.001$). The variance in IQ across sites was less in healthy controls compared to patients with schizophrenia (mean variance in IQ HC=13.14 sd=2.85, Sz=16.53 sd=3.31, t(27)=-2.94, $p<0.01$). The differences in IQ and variance in IQ remain significant with exclusion of the ASRB data, (mean IQ HC=110 sd=6.02, Sz=93 sd=6.89, t(27)=5.85, $p<0.001$, mean variance in IQ HC=14.33 sd=2.65, Sz=17.50 sd=3.41, t(27)=-2.24, $p<0.05$).

DTI and IQ

The white matter tracts included in the gFA and LA-gFA princpal components analyses are outlined in supplementary table 2. The scree plots from the principal component analysis for each site provided evidence for a strong single latent factor for both global FA (gFA) and the six long association tracts (LA-gFA) in each case, figure 1. To determine the variances in IQ explained by global and long association white matter tracts, a regression analysis was carried out for gFA and LA-gFA separately, controlling for both age and gender, in patients and healthy participants, on an site-by-site basis.

gFA analyses

Meta-analytical results from the regression analysis for gFA showed that global white matter accounted for a significant amount of variance in IQ in the overall sample (3% variance, Hedges' g ES=0.27, 95% CI=0.17-0.35, $p<0.001$, see figure 2, supplementary table 4).

When considered separately, similar effects were observed in both the healthy participant subgroup (ES=0.32, 95% CI=0.18-0.45, p<0.001) and patient subgroup (0.20, 95% CI=0.05-0.35, p<0.01), figure 3.

A between group analsysis was undertaken to estimate whether the strenght of between white matter and IQ was different in patients versus healthy participants. No effect of diagnosis was observed (mixed model between-groups $x^2(1)=1.29$, p=.26), indicating that the amount of variance in IQ explained by gFA was comparable between these groups.

Given the differences in developmental stage of two samples that included adolescent participants (Oxford and Madrid) versus the result of the cohort, we re-ran the analysis excluding these two sites (healthy participants n=120, patients n=84). Removal of these adolescent datasets did not change the results of the meta-analysis - comparable findings were obtained for the sample overall (Hedges' g ES=0.27, 95% CI=0.17-0.38, p<0.001), healthy participant subgroup (Hedges' g ES=0.32, 95% CI=0.18-0.46, p<0.001), and patient subgroup (Hedges' g ES=0.21, 95% CI=0.06-0.37, p<0.01). Furthermore, we observed higher IQ in the patient group across the ASRB sites. Again, removing this site from the analysis did not change the observed effect size for the healthy participant subgroup (Hedges' g ES=0.33, 95% CI=0.18-0.48, p<0.001) and patient subgroup (Hedges' g ES=0.21, 95% CI=0.006-0.40, p<0.05).

Due to the variance in effect size across sites, a leave-one-out analysis was carried out to determine if the observed results were driven by single sites. The leave-one-out cross validation requires multiple iterations of the meta-analysis on all the data except for the one site excluded per iteration (n-1). A meta-analysis was then carried out on the mean and standard deviation of the observed effect size for each iteration, with one study ommited for the analysis. The results of gFA leave-one-out analysis remain significant for each iteration, with the mean ES=0.25, range=0.18-0.34 for the full sample, ES=0.29, range=0.26-0.34 for healthy controls, and ES=0.20, range=0.18-0.22 for patients, figure 4a, supplementary table 7.

LA-gFA analyses

To specifically test for a relationship between cognition and long association fibre tracts previously hypothesised in the literature to be involved in cognitive performance, a single latent FA factor was generated for the six long association tracts, identified above, and termed LA-gFA. Similarly to global white matter microstructure, LA-gFA accounted for a significant amount of variance in IQ in the full sample (3.5% variance, Hedges' g ES=0.28, 95% CI=0.18-0.37, p<0.001), figure 3. This significant effect for LA-gFA was also observed separately in the healthy participant subgroup (Hedges' g

ES=0.31, 95% CI=0.18-0.44, p<0.001) and patient subgroup (Hedges' g ES=0.23, 95% CI=0.09-0.38, p<0.01). The meta-analytic results for LA-gFA are outlined in supplementary table 5. The between-sample LA-gFA meta-analysis results again indicate that there was no significant difference in the observed effect size between the healthy participant and patient subgroups (x^2(1)=0.55, p=0.46). As with gFA, these results did not change after removing adolescent populations (Hedges' g overall sample ES=0.29 95% CI=0.18-0.40, healthy participant ES=0.33 95% CI=0.19-0.47, and patient ES=0.23 95% CI=0.08-0.39 subgroups), with no observed diagnostic effect (x^2(1) =0.85, p=0.36). Similarly, removal of the ASRB data did not significantly change the effect size for both healthy participants (Hedges' g ES=0.32, 95% CI=0.18-0.47, p<0.001), and patients (Hedges' g ES=0.27, 95% CI=0.07-0.47, p<0.01), with no significant diagnostic effect (x^2(1) =0.18, p=0.68). The comparable findings between gFA and LA-gFA are perhaps not surprising given the strong positive correlation between these components (see supplementary table 6). Given this, to determine whether the effects observed for gFA were driven by long association tracts, we re-calculated the gFA component to exclude the six long association tracts on which the LA-gFA was based. The results obtained were largely unchanged, both for the whole group analysis (3% variance, Hedges' g ES=0.29, 95% CI=0.19-0.39, p<0.001) and separately for the healthy participant subgroup (Hedges' g ES=0.30, 95% CI=0.17-0.44, p<0.001) and patient subgroup (Hedges' g ES=0.27, 95% CI=0.13-0.42, p<0.001). Finally, as per the gFA analyses, a leave-one-out analysis was also undertaken. Here again, the results remain unchanged (mean ES=0.27, range=0.21-0.33 for the full sample, ES=0.31, range=0.29-0.33 for healthy controls, and ES=0.23, range=0.21-0.27 for patients, figure 4b, supplementary table 8).

Assocation between gFA/LAgFA and IQ in males & females

To determine the effects of gender on the relationship between white matter and IQ, a further meta-analysis was carried out. Similar results were observed between males and females in gFA (males Hedges' g ES=0.36, CI=0.23-0.48, p<0.001, females ES=0.39, CI=0.22-0.55, p<0.001), with no significant difference, x^2(1)=0.088, p=0.77 (supplementary figure 1a, supplementary table 9). For gFA, female patients had the largest observed effect size, although this was not significantly different compared to male patients (female Sz Hedges' g ES=0.45, CI=0.25-0.65, p<0.001, male HC ES=0.25, CI=0.07-0.43, p<0.01, x^2(1)=2.14, p=0.14). Similarly, there was no effect of gender in the healthy control sample (female HC Hedges' g ES=0.27, CI=0.06-0.48, p<0.05, male HC ES=0.39, CI=0.20-0.47, p<0.001, x^2(1)=0.68, p=0.14).

Likewise for LAgFA there was no significant difference in the observed effect sizes for males and females (males Hedges' g ES=0.33, CI=0.21-0.46, p<0.001, females ES=0.37, CI=0.20-0.53, p<0.001, supplementary figure 1b, supplementary table 10). Female patients had the largest observed effect

size for LA-gFA, although this was not significantly different compared to male patients (female Sz Hedges' g ES=0.39, CI=0.10-0.68, p<0.01, male HC ES=0.19, CI=0.01-0.37, p<0.01, $x^2(1)=1.35$, $p=0.26$). Similarly, there was no effect of gender in the healthy control sample (female HC Hedges' g ES=0.31, CI=0.10-0.52, p<0.01, male HC ES=0.38, CI=0.20-0.57, p<0.001, $x^2(1)=0.27$, $p=0.60$).

Association between diffusion MRI secondary parameters and IQ

Secondary diffusion MRI parameters were available for a subset of sites (ASRB, Edinburgh, Dublin, HUBIN, MCPR, Galway) which included 397 healthy controls and 467 patients with schizophrenia. Meta-analysis, reported in supplementary table 11, show that radial diffusivity had the largest effect size for both global and long association tracts across the full sample (gRD ES=0.33, CI=0.13-0.52, p=0.001 and LA-gRD ES=0.34, CI=0.08-0.0.52, p=0.01). Standardized Beta coefficients from this analysis is reported in supplementary table 12.

Discussion

This study sought to characterise the relationship between white matter microstructure and IQ, and to compare this association between patients with schizophrenia and healthy participants. We carried out a meta-analysis of datasets from participating ENIGMA groups, analysed according to a common analysis pipeline, to assess the relationship between white matter microstructure and IQ in patients with schizophrenia and healthy participants. Our findings indicated that global white matter microstructure accounted for a significant amount of variation in IQ (ES=0.27), both in patients with schizophrenia and healthy participants, with the size of association observed to be comparable between groups. Comparable results were obtained based on either global white matter values (ES=0.27), or six regional association white matter tracts (ES=0.28) which connect frontal, parietal and temporal lobes and previously hypothesised as involved in IQ. These findings were unequivocal, supporting the value of meta-analysis based on harmonized pipelines and large datasets.

The results of this ENIGMA meta-analysis consistently showed a pattern of significant (albeit modest) associations between white matter FA and IQ in both patients and healthy participants. Robust evidence of association between variation in IQ and variation in white matter structural connectivity was found, with similar effect sizes observed in patients and healthy participant cohorts. A landmark review carried out by Deary *et al* (24) suggested that intelligence is regulated by a widely distributed complex neurological network. Our study provides empirical evidence for this claim in the largest IQ study undertaken to date, consistent with previous studies linking white matter microstructure to processing speed (a cognitive variables highly correlated with IQ; (18, 22, 27). Collectively, these results indicate that global white matter provides a neural network to support the functional cortical communication required for general cognitive performance. The similar effect sizes observed in both global and long association fibre-based measures of FA underline the nature of this relationship as a global phenomenon rather than a regionally specific association.

Previous studies had focused mainly on individual white matter tracts, including fronto-parietal white matter (22, 28), cingulate (21, 29, 30), uncinate fasciculus (20), fornix (19), and corpus callosum (31). A significant positive correlation between IQ in fronto-parietal white matter (28), uncinate fasciculus (20), and cingulate bundle (21, 30) was frequently observed in schizophrenia, with negative or no significant associations reported in healthy participants. The heterogeneity of results between studies was most likely due to small sample sizes, and methodological differences that limited replicability of results (19-22, 28-32). Here we have overcome the limitation of small sample sizes by using a harmonized processing DTI pipeline and statistical analysis on over 1,700 participants. We also conclude that the findings reported here are not driven any single site (based

on the leave-one-out analyses for both gFA and LA-gFA) and can therefore be expected to generalize to independent samples. In addition, these findings did not appear to be explained by the higher proportion of males in the total sample as we have shown that the association between white matter microstructure and IQ is not significantly different between males and females.

The relationship between white matter microstructure and IQ in patients versus controls

Our results indicate that the relationship between structural connectivity and higher cognitive function is broadly comparable between patient and control groups, with no differences in effect sizes observed. We (6) previously reported widespread white matter deficits in schizophrenia that spanned 19 white matter tracts and hypothesised that in schizophrenia these may predict deficits in cognitive performance more strongly than for variance in cognitive performance in the normal population, as suggested by previous, albeit smalls scale, studies (20-22, 28, 30). By contrast, however, we observed similar effects between patients and healthy participants. This finding suggests that individual variances of low to high efficient transfer of information across white matter tracts is associated with a range of lower to higher cognitive functioning, irrespective of diagnosis. As such, patients with schizophrenia occupied the lower quadrant of the correlation matrix between white matter microstructure and IQ. We speculate, based on these results, that a common neurodevelopment process and cytoarchitecture predicts outcomes in cognitive performance, independent of a clinical diagnosis. However, future studies of the genetic and neurodevelopment associations between schizophrenia, white matter, and measures of cognitive ability will be needed to address these questions.

Patients in the ASRB dataset had an average IQ value of 105. Generally, patients with schizophrenia consistently demonstrate a medium-sized impairment in IQ (33), with an 8-point IQ deficit observed in the premorbid stage (33), and 14-21 point IQ deficit amongst those with first episode and chronic schizophrenia (34-36). Furthermore, lower IQ is associated with increased risk of schizophrenia (37). To determine if the ASRB patient IQ (above average norms) was confounding any diagnostic effect, the analysis was re-run without this data. The effect size observed for the patient group, for both gFA and LA-gFA, did not significantly change, supporting the hypothesis that the association between white matter and IQ is independent of diagnosis.

Kelly et al. reported patients with schizophrenia had significantly higher mean diffusivity and radial diffusivity across the majority of white matter tracts. Higher radial diffusivity, which underlies changes in fractional anisotropy, is indicative of microstructural alterations. Specifically, it provides an index of diffusion in an orientation perpendicular to a white matter tract. Our findings indicate both higher FA, and related to this, lower RD is associated with higher cognitive function in both

patients and controls. Similar effect sizes were observed for the association between radial diffusivity and IQ in both patients and controls. While the precise biological interpretation of changes in radial diffusivity must be done cautiously, however previous studies have speculated that radial diffusivity is associated with demyelination (38). Increased radial diffusivity associated with demyelination supports our findings that efficient global structural connectivity facilitates higher cognitive function, independent of diagnosis.

Strengths & Limitations

In this study, we adopted a 'prospective' meta-analytic approach that analysed the relationship between IQ and DTI based on a well validated and harmonised ENIGMA DTI analysis pipeline carried out in a large sample of 1,717 participants. Doing so overcomes many of the significant limitations in previous studies by minimising sources of heterogeneity, and potential for consequent false positive/negatives findings. However, future analysis could also include methods to incorporate harmonised measures of environmental factors, such as educational level, socio-economic status, general health and lifestyle, which may impact cognitive outcomes. ENIGMA DTI pipelines incorporate tract based spatial statistics (14), which is a widely used method for voxel-based analysis of white matter tracts. Although tensor based limitations have been widely reported, i.e. it does not capture all information on white matter microstructure, such as myelination, axonal packing density, or neuro-inflammation. DTI remains the most consistently used method in diffusion MRI analysis, and pending a general consensus on non-tensor based processing methods that are void of potential artifacts, the analysis carried out here is the most advanced that definitively supports the structural underpinnings of cognitive performance. During image preprocessing, DTI data was corrected for motion induced artifacts, however studies have shown that some white matter tracts may be more sensitive to microscopic head movements which may produce spurious group differences (39). To overcome motion induced variances, previous single site studies have included a metric of motion as a covariate in the analysis (39, 40). Further development of these methods would be required for implementation in multi-site analysis within large consortia.

Here, we used a principal component analysis to derive components for global and long association tract FA values. While this eliminates the need for multiple comparison correction, it reduces the ability to detect a possible, albeit unlikely, association between cognition and specific individual white matter tracts. Previous studies used similar PCA analyses to assess the relationship between global neural underpinnings of functional measures (17, 41).

While we have unequivocally shown here a relationship between white matter and cognitive ability, further studies are necessary to determine the associations with gray matter measures. Although

this has been more widely studied in the literature, study sample sizes were still limited and methodological issues make it difficult to summarize the findings. The latest ENIGMA study (Grasby et al., under review) shows a strong overlap between the genetic influences on cortical surface area and educational attainment. Similar analysis to that carried out here may help identify cortical regions associated with cognitive deficits observed in schizophrenia. Finally, future analysis is also required to determine if the associations reported here generalise to other psychiatric disorders, although the comparability between patients and controls observed here suggests that this is likely.

Conclusion

This study provides robust evidence that cognitive ability is associated with global structural connectivity, with more efficient white matter microstructure associated with higher IQ. This association was independent of diagnosis: across the distribution of scores on FA and IQ measures, patients tended to have lower FA and lower IQ, healthy participants tended to have higher FA and higher IQ, and the effects size of these associations between FA and IQ were comparable between groups. These findings suggest that a general association between lower FA and lower IQ is likely, with white matter microstructure likely to represent a significant component in the neural basis of IQ.

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Tables & Figures

Tables

Table 1. Demographical data collected from 11 collaborating ENIGMA-Schizophrenia DTI working group sites.

Figures Attached Seperately

Figure Legends

Figure 2. Forest plot for gFA meta-analysis (Hedges' g and 95% CI). There was no significant difference between the observed effect size in patients compared to controls, $x^2(1)=1.3$, $p=0.26$. ┼ indicates Hedges' g subgroup summaries for patients and control groups separately, ♦ represents summary statistics for the full sample.

Figure 3. Forest plot for LA-gFA meta-analysis (Hedges' g and 95% CI). There was no significant difference between the observed effect size in patients compared to controls, $x^2(1)=0.55$, $p=0.46$. ┼ indicates Hedges' g subgroup summaries for patients and control groups separately, ♦ represents summary statistics for the full sample.

Figure 4. Leave-one-out meta-analysis for **a** gFA and **b** LAgFA. For both, 11 separate meta-analyses were carried out with n-1 site. The mean Hedges' g effect size was taken for each meta-analysis with one site omitted for each iteration. The study name corresponds to the results when this site was omitted from the analysis. The association between both gFA and LAgFA with IQ remains significant for each iteration indicating that the results are not driven by a specific site.

Additional figures and tables are in the supplementary data.

		sample size		Mean Age *st. dev*		Mean IQ *st. dev*	
		HC	**SZ**	**HC**	**SZ**	**HC**	**SZ**
ASRB1	Male	16	89	40	39	118	100
	Female	17	32	*14.1*	*10.9*	*11*	*17*
ASRB2	Male	41	54	41	38	115	105
	Female	38	31	*13.8*	*10.4*	*11*	*13*
ASRB3	Male	9	12	44	42	113	112
	Female	9	5	*13.6*	*8.7*	*12*	*12*
ASRB4	Male	15	28	37	39	120	101
	Female	14	11	*13.7*	*10.4*	*8*	*17*
ASRB5	Male	18	42	40	40	118	105
	Female	20	22	*13.9*	*10.4*	*13*	*14*
Edin	Male	19	17	37	35	116	105
	Female	17	11	*15.2*	*10.1*	*11*	*16*
Dublin	males	27	22	35	44	118	91
	females	33	6	*12.1*	*11.1*	*16*	*14*
Galway	males		20		34		92
	females		5		*11.1*		*21*
HUBIN	male	20	22	54	52	104	88
	female	12	5	*8.96*	*7.5*	*18*	*18*
MPRC	male	26	21	39	37	99	91
	female	46	10	*14.3*	*12.5*	*18*	*15*
TOP	male	137	18	32	29	113	97
	female	99	11	*7.6*	*8.4*	*11*	*15*
MCIC	males	72	69	31	33	115	98
	females	41	26	*10.9*	*11.4*	*14*	*19*
COBRE	males	62	72	39	39	111	99
	females	22	22	*11.9*	*13.8*	*13*	*17*
Madrid	male	53	31	13	17	111	80
	female	31	10	*4.3*	*3.3*	*15*	*25*
Oxford	males	24	18	13	14	109	91
	females	19	18	*1.2*	*1.4*	*13*	*15*
		957	**760**	**36**	**36**	**113**	**97**
				10.1	***9.1***	***6***	***8***

Table 1. Data collected from 11 collaborating ENIGMA-Schizophrenia DTI working group. The final sample size consisted of 1049 healthy participants and 798 patients with schizophrenia. *indicates sites with data from adolescent participants. **ASRB**=Australian Schizophrenia Research Bank, **EDIN**=Edinburgh, **HUBIN**=Human Brain Informatics, **MPRC**=Maryland Psychiatric Research Center, **MCIC**=MIND Clinical Imaging Consortium, **COBRE**= Center for Biomedical Research Excellence.

Figure 1a

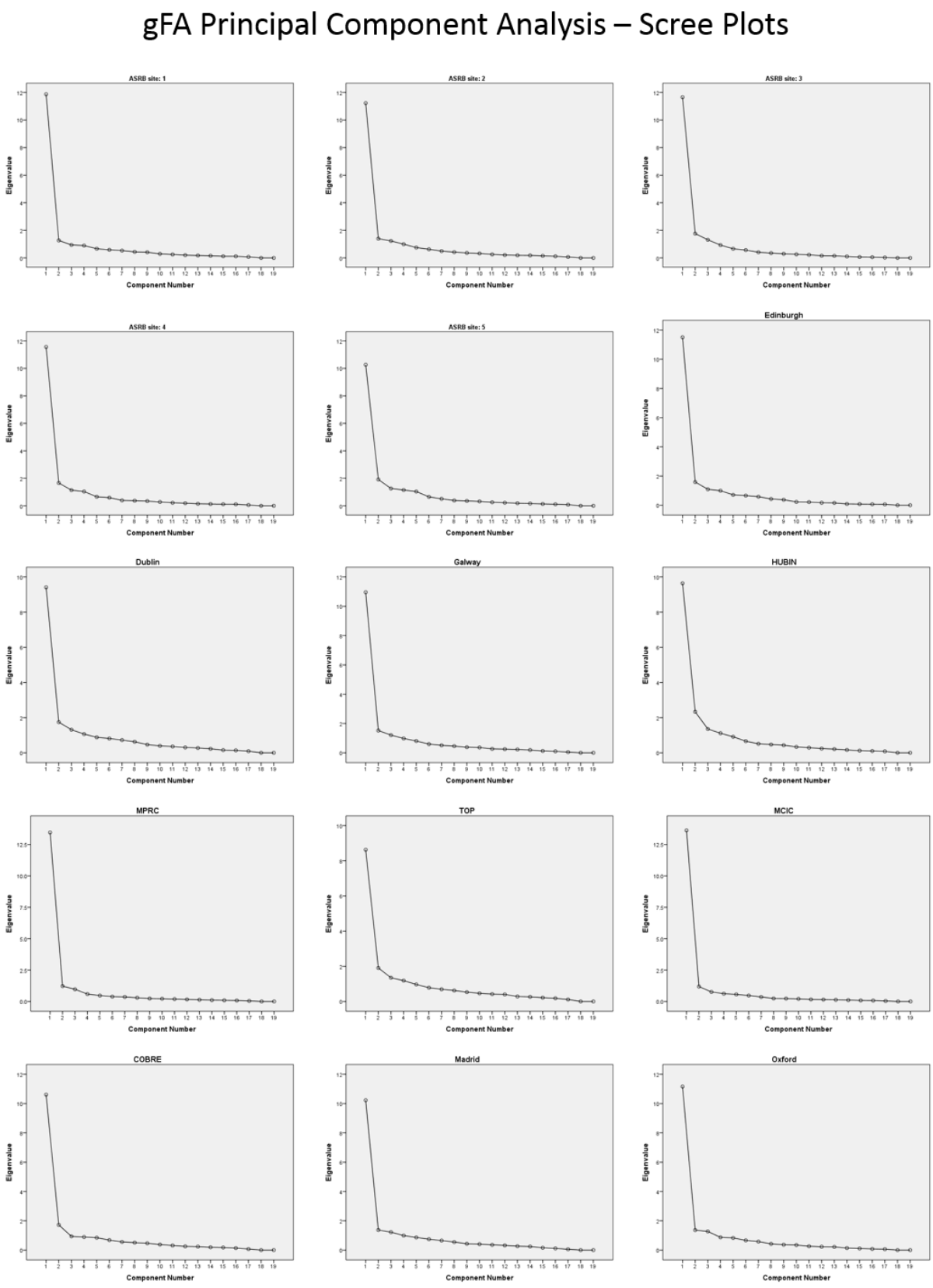

gFA Principal Component Analysis – Scree Plots
ASRB site: 1
ASRB site: 2
ASRB site: 3
ASRB site: 4
ASRB site: 5
Edinburgh
Dublin
Galway
HUBIN
MPRC
TOP
MCIC
COBRE
Madrid
Oxford
Eigenvalue
Component Number

Figure 1b

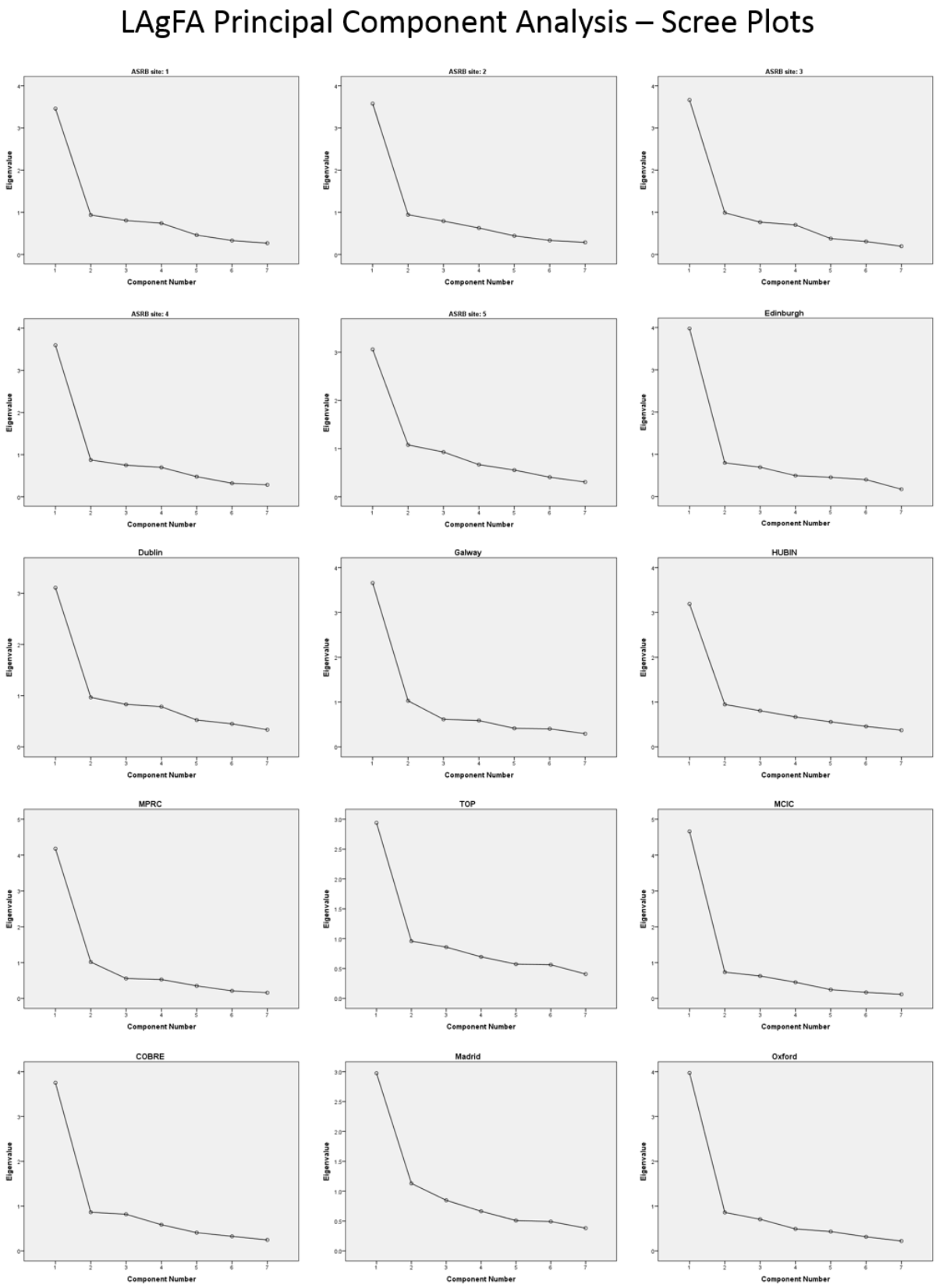

LAgFA Principal Component Analysis – Scree Plots
ASRB site: 1
ASRB site: 2
ASRB site: 3
ASRB site: 4
ASRB site: 5
Edinburgh
Dublin
Galway
HUBIN
MPRC
TOP
MCIC
COBRE
Madrid
Oxford
Eigenvalue
Component Number

Figure 2

Group by Diagnosis	Study Name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	p-Value	Z-Value
HC	ASRB-1	0.138	0.366	0.134	-0.579	0.856	0.706	0.378
HC	ASRB-2	0.324	0.233	0.054	-0.132	0.779	0.164	1.392
HC	ASRB-3	0.121	0.518	0.268	-0.894	1.135	0.816	0.233
HC	ASRB-4	0.285	0.397	0.157	-0.493	1.062	0.473	0.718
HC	ASRB-5	0.280	0.342	0.117	-0.390	0.949	0.413	0.819
HC	EDIN	0.206	0.350	0.123	-0.480	0.893	0.556	0.589
HC	Dublin	0.000	0.265	0.070	-0.519	0.519	1.000	0.000
HC	HUBIN	0.087	0.372	0.138	-0.641	0.816	0.814	0.235
HC	MCPR	0.393	0.246	0.060	-0.088	0.875	0.109	1.601
HC	TOP	0.380	0.133	0.018	0.118	0.641	0.004	2.846
HC	MCIC	0.485	0.196	0.039	0.100	0.869	0.014	2.468
HC	COBRE	0.398	0.227	0.051	-0.046	0.843	0.079	1.756
HC	Madrid	0.323	0.225	0.051	-0.118	0.765	0.151	1.435
HC	Oxford	0.175	0.318	0.101	-0.447	0.798	0.581	0.552
HC		0.316	0.067	0.005	0.185	0.448	0.000	4.716
Sz	ASRB-1p	0.228	0.185	0.034	-0.135	0.591	0.218	1.231
Sz	ASRB-2p	0.035	0.221	0.049	-0.398	0.468	0.874	0.159
Sz	ASRB-3p	0.310	0.542	0.294	-0.752	1.373	0.567	0.572
Sz	ASRB-4p	0.197	0.335	0.112	-0.460	0.854	0.557	0.588
Sz	ASRB-5p	0.335	0.260	0.067	-0.174	0.845	0.197	1.291
Sz	EDINp	1.566	0.518	0.269	0.550	2.581	0.003	3.021
Sz	Dublinp	0.298	0.405	0.164	-0.496	1.091	0.462	0.736
Sz	Galp	0.362	0.434	0.188	-0.489	1.213	0.404	0.834
Sz	HUBINp	0.174	0.410	0.168	-0.629	0.978	0.671	0.425
Sz	MCPRp	0.107	0.379	0.143	-0.635	0.849	0.778	0.282
Sz	TOPp	0.278	0.396	0.157	-0.499	1.055	0.484	0.701
Sz	MCICp	0.109	0.209	0.044	-0.300	0.519	0.601	0.523
Sz	COBREp	0.125	0.210	0.044	-0.287	0.537	0.551	0.596
Sz	Madridp	0.108	0.325	0.106	-0.529	0.745	0.740	0.332
Sz	Oxfordp	0.063	0.348	0.121	-0.620	0.745	0.857	0.180
Sz		0.201	0.076	0.006	0.053	0.350	0.008	2.660
Overall		0.266	0.050	0.003	0.167	0.364	0.000	5.294

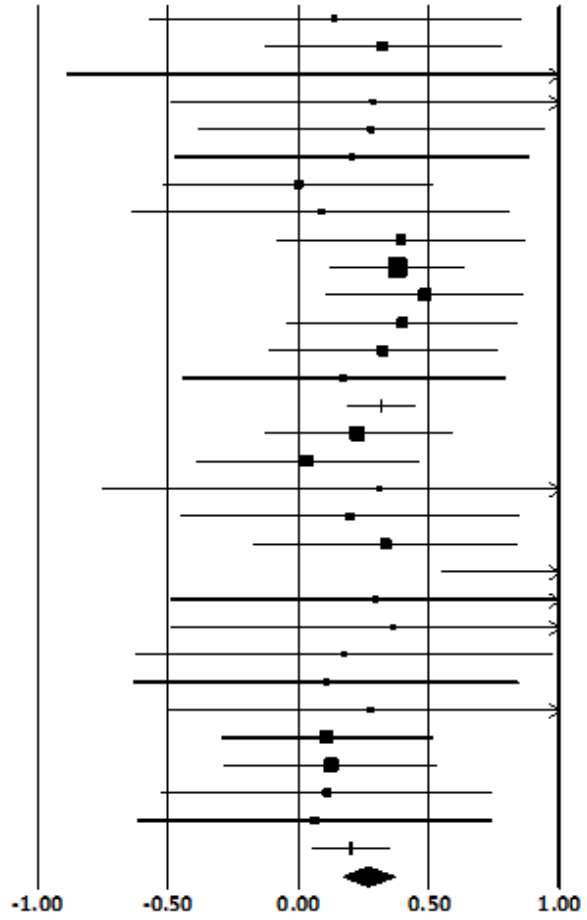


Figure 3

Group by Diagnosis	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
HC	ASRB-1	0.039	0.356	0.127	-0.659	0.737	0.110	0.913
HC	ASRB-2	0.464	0.233	0.054	0.007	0.921	1.988	0.047
HC	ASRB-3	0.182	0.494	0.244	-0.787	1.150	0.367	0.713
HC	ASRB-4	0.062	0.381	0.145	-0.686	0.809	0.161	0.872
HC	ASRB-5	0.187	0.332	0.111	-0.465	0.838	0.561	0.575
HC	EDIN	0.062	0.341	0.116	-0.606	0.729	0.182	0.856
HC	Dublin	0.208	0.263	0.069	-0.307	0.724	0.793	0.428
HC	HUBIN	0.942	0.402	0.162	0.154	1.730	2.343	0.019
HC	MCPR	0.177	0.239	0.057	-0.292	0.645	0.739	0.460
HC	TOP	0.374	0.133	0.018	0.114	0.634	2.815	0.005
HC	MCIC	0.485	0.195	0.038	0.102	0.867	2.486	0.013
HC	COBRE	0.354	0.224	0.050	-0.084	0.793	1.584	0.113
HC	Madrid	0.125	0.221	0.049	-0.307	0.558	0.567	0.571
HC	Oxford	0.217	0.312	0.098	-0.395	0.829	0.696	0.487
HC		0.309	0.066	0.004	0.178	0.439	4.646	0.000
Sz	ASRB-1p	0.384	0.186	0.035	0.019	0.749	2.061	0.039
Sz	ASRB-2p	0.009	0.219	0.048	-0.420	0.438	0.040	0.968
Sz	ASRB-3p	0.234	0.511	0.261	-0.768	1.236	0.458	0.647
Sz	ASRB-4p	0.176	0.328	0.107	-0.467	0.819	0.537	0.592
Sz	ASRB-5p	0.088	0.253	0.064	-0.408	0.585	0.349	0.727
Sz	EDINp	1.579	0.501	0.251	0.598	2.561	3.155	0.002
Sz	Dublinp	0.205	0.391	0.152	-0.560	0.970	0.525	0.600
Sz	Galp	0.122	0.413	0.171	-0.688	0.932	0.295	0.768
Sz	HUBINp	0.185	0.398	0.158	-0.594	0.965	0.465	0.642
Sz	MCPRp	0.542	0.382	0.146	-0.207	1.291	1.418	0.156
Sz	TOPp	0.000	0.381	0.145	-0.747	0.747	0.000	1.000
Sz	MCICp	0.342	0.210	0.044	-0.069	0.754	1.631	0.103
Sz	COBREp	0.064	0.208	0.043	-0.344	0.471	0.305	0.760
Sz	Madridp	0.351	0.323	0.104	-0.283	0.984	1.085	0.278
Sz	Oxfordp	0.108	0.341	0.116	-0.561	0.776	0.316	0.752
Sz		0.234	0.075	0.006	0.088	0.381	3.135	0.002
Overall		0.276	0.050	0.002	0.179	0.373	5.555	0.000

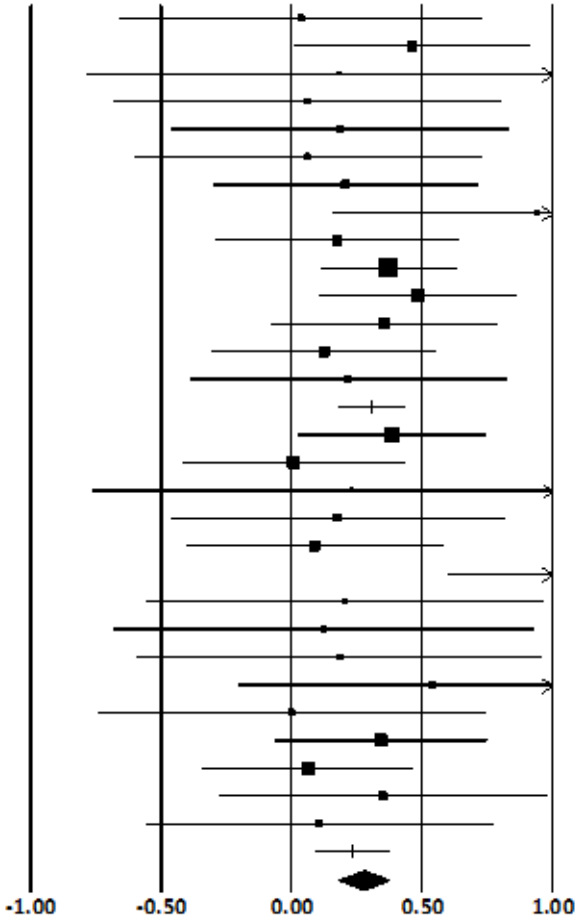


Figure 4a

Group by Diagnosis	Study name	Statistics for each study						
		Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
HC	ASRB	0.295	0.062	0.004	0.173	0.417	4.746	0.000
HC	Cobre	0.279	0.059	0.003	0.163	0.395	4.727	0.000
HC	Dublin	0.336	0.061	0.004	0.217	0.455	5.546	0.000
HC	Edin	0.292	0.057	0.003	0.180	0.404	5.123	0.000
HC	Galway	0.289	0.056	0.003	0.179	0.399	5.151	0.000
HC	HUBIN	0.298	0.057	0.003	0.185	0.411	5.187	0.000
HC	Madrid	0.286	0.059	0.003	0.171	0.401	4.883	0.000
HC	MCIC	0.266	0.059	0.004	0.150	0.382	4.490	0.000
HC	MCPR	0.282	0.058	0.003	0.168	0.396	4.852	0.000
HC	Oxford	0.293	0.057	0.003	0.181	0.405	5.141	0.000
HC	Top	0.262	0.064	0.004	0.137	0.387	4.097	0.000
HC		0.289	0.018	0.000	0.254	0.324	16.280	0.000
Sz	ASRBp	0.207	0.085	0.007	0.040	0.374	2.434	0.015
Sz	Cobrep	0.214	0.070	0.005	0.078	0.350	3.076	0.002
Sz	Dublinp	0.196	0.067	0.005	0.064	0.328	2.921	0.003
Sz	Edinp	0.175	0.066	0.004	0.047	0.303	2.671	0.008
Sz	Galwayp	0.198	0.066	0.004	0.069	0.327	3.001	0.003
Sz	HUBINp	0.204	0.066	0.004	0.074	0.334	3.071	0.002
Sz	Madridp	0.208	0.066	0.004	0.078	0.338	3.131	0.002
Sz	MCICp	0.216	0.069	0.005	0.080	0.352	3.115	0.002
Sz	MCPRp	0.206	0.066	0.004	0.077	0.335	3.122	0.002
Sz	Oxfordp	0.211	0.067	0.004	0.080	0.342	3.155	0.002
Sz	Topp	0.200	0.066	0.004	0.071	0.329	3.031	0.002
Sz		0.203	0.021	0.000	0.163	0.243	9.880	0.000
Overall		0.252	0.013	0.000	0.226	0.278	18.776	0.000

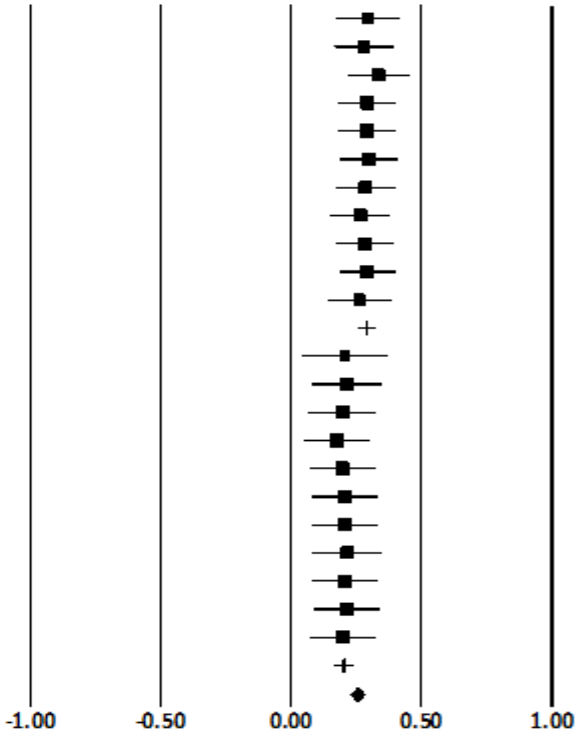
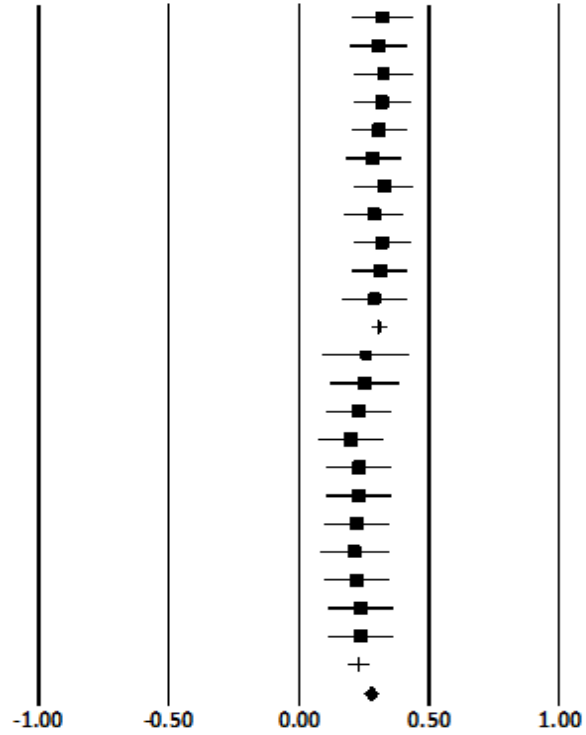


Figure 4b

Group by Diagnosis	Study name	Statistics for each study							Mean and 95% CI
		Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
HC	ASRB	0.322	0.062	0.004	0.201	0.443	5.199	0.000	
HC	Cobre	0.305	0.058	0.003	0.192	0.418	5.289	0.000	
HC	Dublin	0.325	0.060	0.004	0.207	0.443	5.404	0.000	
HC	Edin	0.318	0.057	0.003	0.207	0.429	5.601	0.000	
HC	Galway	0.309	0.056	0.003	0.200	0.418	5.552	0.000	
HC	HUBIN	0.286	0.057	0.003	0.175	0.397	5.038	0.000	
HC	Madrid	0.326	0.058	0.003	0.212	0.440	5.609	0.000	
HC	MCIC	0.288	0.059	0.003	0.172	0.404	4.880	0.000	
HC	MCPR	0.319	0.058	0.003	0.206	0.432	5.531	0.000	
HC	Oxford	0.312	0.057	0.003	0.201	0.423	5.495	0.000	
HC	Top	0.290	0.063	0.004	0.166	0.414	4.583	0.000	
HC		0.309	0.018	0.000	0.275	0.344	17.556	0.000	
Sz	ASRBp	0.257	0.087	0.008	0.087	0.427	2.959	0.003	
Sz	Cobrep	0.253	0.069	0.005	0.118	0.388	3.672	0.000	
Sz	Dublinp	0.230	0.066	0.004	0.100	0.360	3.474	0.001	
Sz	Edinp	0.200	0.065	0.004	0.073	0.327	3.084	0.002	
Sz	Galwayp	0.232	0.065	0.004	0.104	0.360	3.565	0.000	
Sz	HUBINp	0.231	0.066	0.004	0.103	0.359	3.525	0.000	
Sz	Madridp	0.222	0.066	0.004	0.093	0.351	3.376	0.001	
Sz	MCICp	0.213	0.068	0.005	0.079	0.347	3.112	0.002	
Sz	MCPRp	0.219	0.065	0.004	0.091	0.347	3.365	0.001	
Sz	Oxfordp	0.236	0.066	0.004	0.107	0.365	3.577	0.000	
Sz	Topp	0.238	0.065	0.004	0.110	0.366	3.645	0.000	
Sz		0.229	0.020	0.000	0.189	0.269	11.265	0.000	
Overall		0.275	0.013	0.000	0.249	0.301	20.644	0.000	



The relationship between white matter microstructure and general cognitive ability in patients with schizophrenia and healthy participants in the ENIGMA consortium

Supplementary Material

Tables

Supplementary Table 1. DTI acquisition protocols for contributing ENIGMA-Schizophrenia working group site

Supplementary Table 2. List of white matter tracts included in the principal component analysis to derive a single latent component for global fractional anisotropy (gFA) and six long association tracts (LA-gFA).

Supplementary Table 3. Total percent variance explained for gFA and LA-gFA first un-rotated principal component

Supplementary table 4. gFA meta-analysis results using a random effects model.

Supplementary table 5. LAgFA meta-analysis results using a random effects model.

Supplementary Table 6. Pearson's correlation coefficient for gFA and LA-gFA components. cc=correlation coefficient.

Supplementary table 7. Leave-one-out meta-analysis for gFA.

Supplementary table 8. Leave-one-out meta-analysis for LAgFA.

Supplementary table 9. Meta-analysis results for gFA and IQ in males & females.

Supplementary table 10. Meta-analysis results for LAgFA and IQ in males & females.

Supplementary table 11. Meta-analysis results for secondary diffusion MRI parameters.

Supplementary table 12. Per-Site Regression Standardized Beta Coefficients for secondary diffusion MRI parameters.

Figures

Supplementary Figure 1. Sex dependent meta-analysis results for **a** gFA and **b** LAgFA. There was no significant difference in the observed Hedges' g effect size for gFA between males (ES=0.35, CI=0.23-0.48) and females (ES=0.39, CI=0.22-0.55), $x^2(1)=0.09$ $p=0.77$. Similarly for LAgFA there was no significant difference in the observed Hedges' g effect size for males (ES=0.33, CI=0.21-0.46) and females (ES=0.37, CI=0.20-0.53), $x^2(1)=0.11$ $p=0.74$.

Study cohort	Scanner	Field Strength	Acquisitions	Voxel Size and Slice thickness (mm)	Gradient directions and b-value (mm/s2)	b=0 scans
ASRB 1	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 2	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 3	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 4	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
ASRB 5	Siemens Avanto	1.5T	1	2.4x2.4x2.4	64 at b	1
EDIN	Siemens	3T	1	2.2x2.5x2.5	56 at	6
Dublin	Philips Achieva	3T	1	2x2x2.3	15 at b=800	1
Galway	Siemens	1.5T	1	2.5x2.5x2.5	64 at	7
HUBIN	GE	3T	1	0.94 x 0.94	60 at	10
MPRC	Siemens Alegra	3T	1	1.7×1.7×4.0	12 at	8
TOP	GE	3T	1	2x2x2.5	30 at	1
MCIC 1	Siemens Sonata	1.5T	1	2x2x2	12 at	1
MCIC 2	Siemens Trio	3T	1	2x2x2	6 at b=1000	1
MCIC 3	Siemens Trio	3T	1	2x2x2	12 at	1
MCIC 4	Siemens Sonata	1.5T	1	2x2x2	60 at b=700	1
COBRE	Siemens TIM Trio	3T	2	2x2x2	30 at b=800	5
Madrid	Philips Intera	1.5T	1	1.75x1.75x2	15 at b=800	1
Madrid	Philips Intera	1.5T	2	2x2x2	32 at b=800	1
Madrid	Philips Intera	1.5T	1	2x2x2	64 at	1
Oxford	Siemens Sonata	1.5T	3	2.5x2.5x2.5	60 at	5

Supplementary Table 1. DTI acquisition protocols for contributing ENIGMA-Schizophrenia working group site. **ASRB**=Australian Schizophrenia Research Bank, **EDIN**=Edinburgh, **HUBIN**=Human Brain Informatics, **MPRC**=Maryland Psychiatric Research Center, **MCIC**=MIND Clinical Imaging Consortium, **COBRE**= Center for Biomedical Research Excellence.

Abbreviation	White Matter Tract
Avg-FA	Average FA
GCC	Genu of Corpus Callosum
BCC	Body of Corpus Callosum
SCC	Splenium of Corpus Callosum
FX	Fornix
ALIC	Anterior Limb of the Internal Capsule*
IC	Internal Capsule
CC	Corpus Callosum
ACR	Arcuate Fasciculus*
SCR	Superior Corona Radiata
PCR	Posterior Corona Radiata
CR	Corona Radiata
PTR	Posterior Thalamic Radiation
SS	Sagittal stratum
EC	External capsule
CGC	Cingulum (cingulate gyrus)*
SLF	Superior Longitudinal Fasciculus*
SFO	Superior Fronto-Occipital Fasciculus
FX-ST	Fornix/Stria Terminalis
IFO	Inferior Fronto Occipital Fasciculus*
UNC	Uncinate Fasciculus*

Supplementary table 2. The 19 white matter tracts which were reported in Kelly et al to have significantly reduced FA in patients with schizophrenia compared to controls. The ENIGMA-DTI protocol outputs average FA for each bilateral white matter tract. The present analysis combined FA from both hemispheres for the tracts listed above to avoid any potential issues of left/right flipping. gFA was computed using a principal component analysis of the tracts listed above. * identifies tracts used to generate LA-gFA.

ENIGMA Site	**PCA total % Variance Explained**	
	gFA	*LA-gFA*
ASRB-1	58	49
ASRB-2	55	51
ASRB-3	57	52
ASRB-4	56	51
ASRB-5	50	44
EDIN	61	57
Dublin	52	46
Galway	63	64
HUBIN	48	50
MPRC	67	67
TOP	44	43
MCIC	52	42
COBRE	58	57
Madrid	55	54
Oxford	70	67
Median	**56**	**51**
Range	**44-70**	**42-67**

Supplementary Table 3. Total percent variance explained for the first unrotated component representing global fractional anisotropy (gFA) and the first unrotated component representing six long association tracts fractional anisotropy (LA-gFA).

	Site	n	Hedge's g	CI Lower	CI Upper	*p*	Z
HC	ASRB-1	33	0.14	-0.58	0.86	0.71	0.38
	ASRB-2	79	0.32	-0.13	0.78	0.16	1.39
	ASRB-3	18	0.12	-0.89	1.13	0.82	0.23
	ASRB-4	29	0.28	-0.49	1.06	0.47	0.72
	ASRB-5	38	0.28	-0.39	0.95	0.41	0.82
	EDIN	36	0.21	-0.48	0.89	0.56	0.59
	Dublin	60	0.00	-0.52	0.52	1.00	0.00
	HUBIN	32	0.09	-0.64	0.82	0.81	0.23
	MCPR	72	0.39	-0.09	0.87	0.11	1.60
	TOP	236	0.38	0.12	0.64	0.00	2.85
	MCIC	113	0.48	0.10	0.87	0.01	2.47
	COBRE	84	0.40	-0.05	0.84	0.08	1.76
	Madrid	84	0.32	-0.12	0.76	0.15	1.44
	Oxford	43	0.18	-0.45	0.80	0.58	0.55
	HC mean	***957***	***0.32***	***0.18***	***0.45***	***<0.001***	***4.72***
SZ	ASRB-1	121	0.23	-0.14	0.59	0.22	1.23
	ASRB-2	85	0.04	-0.40	0.47	0.87	0.16
	ASRB-3	17	0.31	-0.75	1.37	0.57	0.57
	ASRB-4	39	0.20	-0.46	0.85	0.56	0.59
	ASRB-5	64	0.34	-0.17	0.84	0.20	1.29
	EDIN	28	1.57	0.55	2.58	0.00	3.02
	Dublin	28	0.30	-0.50	1.09	0.46	0.74
	Galway	25	0.36	-0.49	1.21	0.40	0.83
	HUBIN	27	0.17	-0.63	0.98	0.67	0.42
	MCPR	31	0.11	-0.64	0.85	0.78	0.28
	TOP	29	0.28	-0.50	1.05	0.48	0.70
	MCIC	95	0.11	-0.30	0.52	0.60	0.52
	COBRE	94	0.13	-0.29	0.54	0.55	0.60
	Madrid	41	0.11	-0.53	0.74	0.74	0.33
	Oxford	36	0.06	-0.62	0.75	0.86	0.18
	SZ mean	***760***	***0.20***	***0.05***	***0.35***	***<0.01***	***2.66***
Overall		**1717**	**0.27**	**0.17**	**0.36**	**<0.001**	**5.29**

Supplementary table 4. gFA meta-analysis results using a random effects model. gFA accounted for a significant amount of variance in IQ in the full sample (average Hedges' g ES=0.27), healthy participant (ES=0.32) and patient (ES=0.20) groups. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

	Site	n	Hedge's g	CI Lower	CI Upper	*p*	Z
HC	ASRB-1	33	0.04	-0.66	0.74	0.91	0.11
	ASRB-2	79	0.46	0.01	0.92	0.05	1.99
	ASRB-3	18	0.18	-0.79	1.15	0.71	0.37
	ASRB-4	29	0.06	-0.69	0.81	0.87	0.16
	ASRB-5	38	0.19	-0.47	0.84	0.57	0.56
	EDIN	36	0.06	-0.61	0.73	0.86	0.18
	Dublin	60	0.21	-0.31	0.72	0.43	0.79
	HUBIN	32	0.94	0.15	1.73	0.02	2.34
	MCPR	72	0.18	-0.29	0.65	0.46	0.74
	TOP	236	0.37	0.11	0.63	0.00	2.81
	MCIC	113	0.48	0.10	0.87	0.01	2.49
	COBRE	84	0.35	-0.08	0.79	0.11	1.58
	Madrid	84	0.13	-0.31	0.56	0.57	0.57
	Oxford	43	0.22	-0.39	0.83	0.49	0.70
	HC mean	***957***	***0.31***	***0.18***	***0.44***	***<0.0001***	***4.65***
SZ	ASRB-1	121	0.38	0.02	0.75	0.04	2.06
	ASRB-2	85	0.01	-0.42	0.44	0.97	0.04
	ASRB-3	17	0.23	-0.77	1.24	0.65	0.46
	ASRB-4	39	0.18	-0.47	0.82	0.59	0.54
	ASRB-5	64	0.09	-0.41	0.58	0.73	0.35
	EDIN	28	1.58	0.60	2.56	0.00	3.16
	Dublin	28	0.21	-0.56	0.97	0.60	0.53
	Galway	25	0.12	-0.69	0.93	0.77	0.30
	HUBIN	27	0.19	-0.59	0.96	0.64	0.47
	MCPR	31	0.54	-0.21	1.29	0.16	1.42
	TOP	29	0.00	-0.75	0.75	1.00	0.00
	MCIC	95	0.34	-0.07	0.75	0.10	1.63
	COBRE	94	0.06	-0.34	0.47	0.76	0.31
	Madrid	41	0.35	-0.28	0.98	0.28	1.08
	Oxford	36	0.11	-0.56	0.78	0.75	0.32
	SZ mean	***760***	***0.23***	***0.09***	***0.38***	***<0.0001***	***3.13***
Overall		**1717**	**0.28**	**0.18**	**0.37**	***<0.0001***	**5.56**

Supplementary table 5. LAgFA meta-analysis results using a random effects model. LA-gFA accounted for a significant amount of variance in IQ in the full sample (average Hedges' g ES=0.28), healthy participant (ES=0.31) and patient (ES=0.23) groups. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

ENIGMA Site	gFA - LA-gFA cc
ASRB-1	0.95
ASRB-2	0.96
ASRB-3	0.96
ASRB-4	0.95
ASRB-5	0.93
EDIN	0.95
Dublin	0.93
Galway	0.96
HUBIN	0.95
MPRC	0.96
TOP	0.92
MCIC	0.91
COBRE	0.97
Madrid	0.96
Oxford	0.98
Median	**0.95**
Range	**0.91-0.98**

Supplementary Table 6. Pearson's correlation coefficient for gFA and LA-gFA components. cc=correlation coefficient.

	Omitted Site	Mean	CI Lower	CI Upper	p	z
HC	ASRB	0.30	0.17	0.42	<0.001	4.75
	Cobre	0.28	0.16	0.39	<0.001	4.73
	Dublin	0.34	0.22	0.45	<0.001	5.55
	EDIN	0.29	0.18	0.40	<0.001	5.12
	Galway	0.29	0.18	0.40	<0.001	5.15
	HUBIN	0.30	0.19	0.41	<0.001	5.19
	Madrid	0.29	0.17	0.40	<0.001	4.88
	MCIC	0.27	0.15	0.38	<0.001	4.49
	MCPR	0.28	0.17	0.40	<0.001	4.85
	Oxford	0.29	0.18	0.40	<0.001	5.14
	Top	0.26	0.14	0.39	<0.001	4.10
	HC mean	**0.29**	**0.25**	**0.32**	**<0.001**	**16.28**
SZ	ASRB	0.21	0.04	0.37	<0.01	2.43
	Cobre	0.21	0.08	0.35	<0.01	3.08
	Dublin	0.20	0.06	0.33	<0.01	2.92
	EDIN	0.18	0.05	0.30	<0.01	2.67
	Galway	0.20	0.07	0.33	<0.01	3.00
	HUBIN	0.20	0.07	0.33	<0.01	3.07
	Madrid	0.21	0.08	0.34	<0.01	3.13
	MCIC	0.22	0.08	0.35	<0.01	3.12
	MCPR	0.21	0.08	0.34	<0.01	3.12
	Oxford	0.21	0.08	0.34	<0.01	3.16
	Top	0.20	0.07	0.33	<0.01	3.03
	SZ mean	**0.20**	**0.16**	**0.24**	**<0.001**	**9.88**
Overall		**0.25**	**0.23**	**0.28**	**<0.001**	**18.78**

Supplementary table 7. Leave-one-out meta-analysis for gFA. For each meta-analysis iteration a single site was omitted to determine if significant findings were driven by a single site. The leave-one-out analysis indicates that for each site omitted the results remain significant with the mean Hedges' g ES=0.25 for the full sample, ES=0.20 for patients, and ES=0.29 for healthy participants, p<0.001. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

	Omitted Site	Mean	CI Lower	CI Upper	p	z
HC	ASRB	0.32	0.20	0.44	<0.001	5.20
	Cobre	0.31	0.19	0.42	<0.001	5.29
	Dublin	0.33	0.21	0.44	<0.001	5.40
	EDIN	0.32	0.21	0.43	<0.001	5.60
	Galway	0.31	0.20	0.42	<0.001	5.55
	HUBIN	0.29	0.17	0.40	<0.001	5.04
	Madrid	0.33	0.21	0.44	<0.001	5.61
	MCIC	0.29	0.17	0.40	<0.001	4.88
	MCPR	0.32	0.21	0.43	<0.001	5.53
	Oxford	0.31	0.20	0.42	<0.001	5.50
	TOP	0.29	0.17	0.41	<0.001	4.58
	HC mean	**0.31**	**0.27**	**0.34**	**<0.001**	**17.56**
SZ	ASRB	0.26	0.09	0.43	<0.001	2.96
	Cobre	0.25	0.12	0.39	<0.001	3.67
	Dublin	0.23	0.10	0.36	<0.001	3.47
	EDIN	0.20	0.07	0.33	<0.001	3.08
	Galway	0.23	0.10	0.36	<0.001	3.57
	HUBIN	0.23	0.10	0.36	<0.001	3.53
	Madrid	0.22	0.09	0.35	<0.001	3.38
	MCIC	0.21	0.08	0.35	<0.001	3.11
	MCPR	0.22	0.09	0.35	<0.001	3.37
	Oxford	0.24	0.11	0.37	<0.001	3.58
	TOP	0.24	0.11	0.37	<0.001	3.64
	SZ mean	**0.23**	**0.19**	**0.27**	**<0.001**	**11.27**
Overall		**0.27**	**0.25**	**0.30**	**<0.001**	**20.64**

Supplementary table 8. Leave-one-out meta-analysis for LAgFA. For each meta-analysis iteration a single site was omitted to determine if significant findings were driven by a single site. The leave-one-out analysis indicates that for each site omitted the results remain significant with the mean Hedges' g ES=0.27 for the full sample, ES=0.23 for patients, and ES=0.31 for healthy participants, p<0.001. HC=healthy control, SZ=patients with schizophrenia, CI=95% confidence intervals.

	Site	Hedge's g	CI Lower	CI Upper	p	z
Female	ASRB-1	0.52	-0.08	1.12	0.09	1.71
	ASRB-2	0.21	-0.28	0.69	0.40	0.84
	ASRB-3	0.27	-0.93	1.46	0.66	0.44
	ASRB-4	0.00	-0.84	0.84	1.00	0.00
	ASRB-5	0.45	-0.19	1.10	0.17	1.37
	EDIN	0.26	-0.60	1.12	0.55	0.59
	Dublin	0.06	-0.59	0.72	0.85	0.19
	HUBIN	1.00	-2.52	4.52	0.58	0.56
	MCPR	0.32	-0.74	1.39	0.55	0.59
	TOP	0.17	-0.37	0.71	0.55	0.60
	MCIC	0.73	0.33	1.13	<0.001	3.54
	COBRE	0.95	0.41	1.50	<0.001	3.43
	Madrid	0.21	-0.41	0.82	0.51	0.66
	Oxford	0.12	-0.51	0.76	0.70	0.38
	Oxford	0.22	-0.45	0.90	0.52	0.65
	mean	**0.39**	**0.22**	**0.55**	**<0.001**	**4.57**
Male	ASRB-1	0.32	-0.08	0.71	0.11	1.58
	ASRB-2	0.29	-0.12	0.70	0.17	1.38
	ASRB-3	0.12	-0.80	1.05	0.80	0.26
	ASRB-4	0.09	-0.53	0.71	0.78	0.28
	ASRB-5	0.30	-0.23	0.82	0.27	1.10
	EDIN	0.93	0.15	1.71	0.02	2.32
	Dublin	0.11	-0.47	0.69	0.71	0.37
	Galway	0.14	-0.82	1.09	0.78	0.28
	HUBIN	0.53	-0.12	1.18	0.11	1.60
	MCPR	1.03	0.36	1.70	0.00	3.01
	TOP	0.28	-0.04	0.60	0.09	1.69
	MCIC	0.53	0.18	0.87	<0.01	3.00
	COBRE	0.40	0.05	0.74	0.03	2.22
	Madrid	0.20	-0.24	0.64	0.37	0.89
	Oxford	0.23	-0.40	0.87	0.47	0.72
	mean	**0.35**	**0.23**	**0.48**	**<0.001**	**5.57**
Overall		**0.37**	**0.27**	**0.47**	**<0.001**	**7.20**

Supplementary table 9. Meta-analysis results for gFA and IQ in males & females. There was no significant difference in the observed Hedges' g effect size for males (ES=0.35, CI=0.23-0.48) and females (ES=0.39, CI=0.22-0.55), $x^2(1)=0.09$ $p=0.77$. CI=95% confidence intervals.

	Site	Hedge's g	CI Lower	CI Upper	p	z
Female	ASRB-1	0.46	-0.14	1.05	0.13	1.51
	ASRB-2	0.27	-0.22	0.75	0.28	1.08
	ASRB-3	0.10	-1.08	1.29	0.86	0.17
	ASRB-4	0.00	-0.84	0.84	1.00	0.00
	ASRB-5	0.26	-0.38	0.89	0.43	0.80
	EDIN	0.25	-0.62	1.11	0.58	0.56
	Dublin	0.09	-0.57	0.74	0.79	0.26
	HUBIN	0.82	-2.47	4.11	0.63	0.49
	MCPR	0.37	-0.70	1.44	0.50	0.67
	TOP	0.09	-0.45	0.63	0.75	0.32
	MCIC	0.76	0.36	1.17	<0.0001	3.67
	COBRE	0.90	0.36	1.44	<0.01	3.28
	Madrid	0.18	-0.44	0.79	0.58	0.56
	Oxford	0.28	-0.36	0.92	0.39	0.85
	Oxford	0.11	-0.57	0.78	0.75	0.31
	mean	**0.37**	**0.20**	**0.53**	**<0.001**	**4.37**
Male	ASRB-1	0.46	0.06	0.85	0.02	2.25
	ASRB-2	0.36	-0.05	0.78	0.09	1.70
	ASRB-3	0.12	-0.80	1.05	0.80	0.26
	ASRB-4	0.00	-0.62	0.62	1.00	0.00
	ASRB-5	0.26	-0.26	0.78	0.33	0.97
	EDIN	0.83	0.06	1.60	0.03	2.13
	Dublin	0.15	-0.43	0.73	0.61	0.51
	Galway	0.06	-0.89	1.01	0.90	0.13
	HUBIN	0.55	-0.11	1.20	0.10	1.64
	MCPR	0.99	0.33	1.66	<0.01	2.93
	TOP	0.21	-0.11	0.53	0.20	1.29
	MCIC	0.54	0.19	0.88	<0.01	3.05
	COBRE	0.33	-0.02	0.68	0.06	1.87
	Madrid	0.00	-0.44	0.44	1.00	0.00
	Oxford	0.23	-0.41	0.86	0.48	0.70
	mean	**0.33**	**0.21**	**0.46**	**<0.001**	**5.23**
Overall		**0.35**	**0.25**	**0.45**	**<0.001**	**6.81**

Supplementary table 10. Meta-analysis results for LAgFA and IQ in males & females. There was no significant difference in the observed Hedges' g effect size for males (ES=0.33, CI=0.21-0.46) and females (ES=0.37, CI=0.20-0.53), $x^2(1)=0.11$ $p=0.74$. CI=95% confidence intervals.

DTI parameter	Sample	n	Hedge's G	CI lower	CI upper	*p*
MD	HC	397	0.25	0.05	0.46	0.01
	Sz	467	0.19	0.00	0.38	0.05
	All	864	0.22	0.08	0.36	<0.01
RD	HC	397	0.37	0.02	0.72	0.04
	Sz	467	0.31	0.07	0.55	0.01
	All	864	0.33	0.13	0.52	<0.01
AD	HC	397	0.32	0.11	0.52	<0.01
	Sz	467	0.07	-0.12	0.25	0.47
	All	864	0.24	0.11	0.37	0.01
LA-gMD	HC	397	0.19	-0.01	0.34	0.07
	Sz	467	0.09	-0.09	0.28	0.33
	All	864	0.14	0.00	0.27	0.05
LA-gRD	HC	397	0.27	-0.08	0.62	0.13
	Sz	467	0.42	0.04	0.80	0.03
	All	864	0.34	0.08	0.60	0.01
LA-gAD	HC	397	0.28	0.08	0.48	0.01
	Sz	467	0.14	-0.05	0.32	0.15
	All	864	0.20	0.06	0.34	<0.01

Supplementary table 11. Meta-analysis results for secondary diffusion MRI parameters. MD=mean diffusivity, RD=radial diffusivity, AD=axial diffusivity, LA=long association tract analysis. The largest effect sizes were observed for measures relating to radial diffusivity (RD & LA-gRD).

	ASRB	EDIN	Dublin	HUBIN	MPRC	Galway
gFA	0.057	0.369	0.037	0.251	0.273	0.193
gMD	-0.053	-0.106	-0.221	-0.344	-0.01	-0.173
gRD	-0.105	-0.245	-0.153	-0.347	-0.423	-0.197
gAD	0.049	0.195	-0.296	-0.153	-0.101	-0.049
LA-gFA	0.139	0.344	0.079	0.253	0.229	0.064
LA-gMD	-0.12	-0.158	-0.135	-0.28	-0.021	-0.077
LA-gRD	-0.063	-0.265	-0.131	-0.324	-0.385	-0.064
LA-gAD	0.088	0.164	-0.114	-0.115	-0.094	-0.033

Supplementary table 12. Per-Site Regression Standardized Beta Coefficients for secondary diffusion MRI parameters. The standardized Beta's reported here support our findings that higher FA is associated with higher cognitive functions, which is primarily driven by increased radial diffusivity.

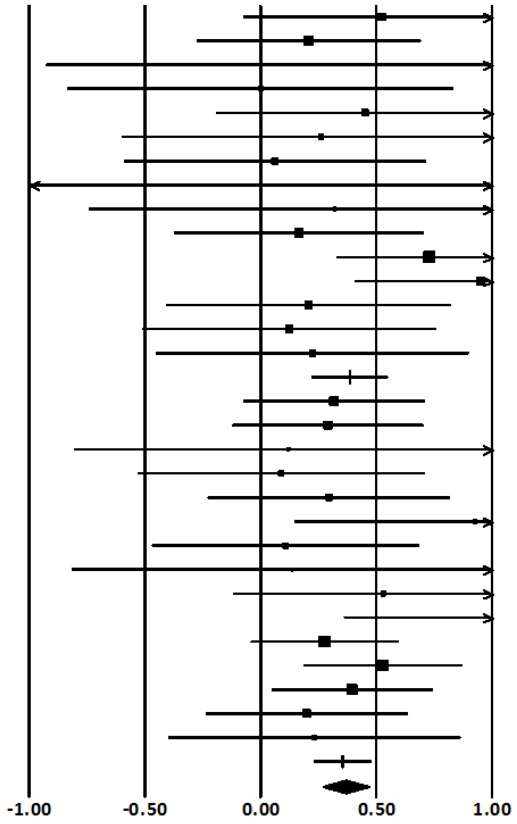
Supplementary Figure 1a.

gFA Females and Males

Group by Sex	Study Name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	p-Value	Z-Value
Female	ASRB1-F	0.523	0.305	0.093	-0.075	1.122	0.087	1.714
Female	ASRB2-F	0.209	0.248	0.061	-0.276	0.694	0.399	0.843
Female	ASRB3-F	0.267	0.610	0.372	-0.928	1.462	0.662	0.437
Female	ASRB4-F	0.000	0.426	0.182	-0.836	0.836	1.000	0.000
Female	ASRB5-F	0.451	0.329	0.108	-0.194	1.096	0.170	1.371
Female	EDIN-F	0.261	0.441	0.194	-0.602	1.125	0.553	0.593
Female	Dublin-F	0.063	0.334	0.111	-0.591	0.716	0.851	0.188
Female	Galway-F	0.999	1.796	3.225	-2.521	4.518	0.578	0.556
Female	HUBIN-F	0.322	0.543	0.294	-0.742	1.385	0.554	0.592
Female	MCPR-F	0.166	0.276	0.076	-0.374	0.707	0.547	0.603
Female	TOP-F	0.730	0.206	0.042	0.326	1.134	0.000	3.542
Female	MCIC-F	0.952	0.278	0.077	0.407	1.497	0.001	3.426
Female	COBRE-F	0.207	0.314	0.099	-0.408	0.823	0.509	0.660
Female	Madrid-F	0.124	0.325	0.106	-0.513	0.761	0.703	0.381
Female	Oxford-F	0.225	0.345	0.119	-0.452	0.901	0.516	0.650
Female		0.386	0.085	0.007	0.221	0.552	0.000	4.570
Male	ASRB1-M	0.318	0.201	0.040	-0.075	0.711	0.113	1.584
Male	ASRB2-M	0.291	0.211	0.044	-0.122	0.704	0.168	1.379
Male	ASRB3-M	0.121	0.472	0.223	-0.805	1.047	0.798	0.257
Male	ASRB4-M	0.088	0.317	0.100	-0.532	0.709	0.780	0.279
Male	ASRB5-M	0.295	0.268	0.072	-0.230	0.821	0.270	1.103
Male	EDIN-M	0.927	0.399	0.159	0.145	1.709	0.020	2.325
Male	Dublin-M	0.108	0.295	0.087	-0.470	0.687	0.714	0.367
Male	Galway-M	0.136	0.486	0.237	-0.817	1.090	0.779	0.280
Male	HUBIN-M	0.531	0.332	0.110	-0.120	1.181	0.110	1.598
Male	MCPR-M	1.027	0.341	0.116	0.359	1.696	0.003	3.011
Male	TOP-M	0.277	0.164	0.027	-0.044	0.598	0.090	1.693
Male	MCIC-M	0.529	0.176	0.031	0.184	0.874	0.003	3.002
Male	COBRE-M	0.395	0.178	0.032	0.046	0.745	0.027	2.219
Male	Madrid-M	0.199	0.223	0.050	-0.239	0.637	0.373	0.892
Male	Oxford-M	0.233	0.323	0.104	-0.399	0.865	0.470	0.723
Male		0.355	0.064	0.004	0.230	0.480	0.000	5.567
Overall		0.366	0.051	0.003	0.267	0.466	0.000	7.197

Statistics for each study

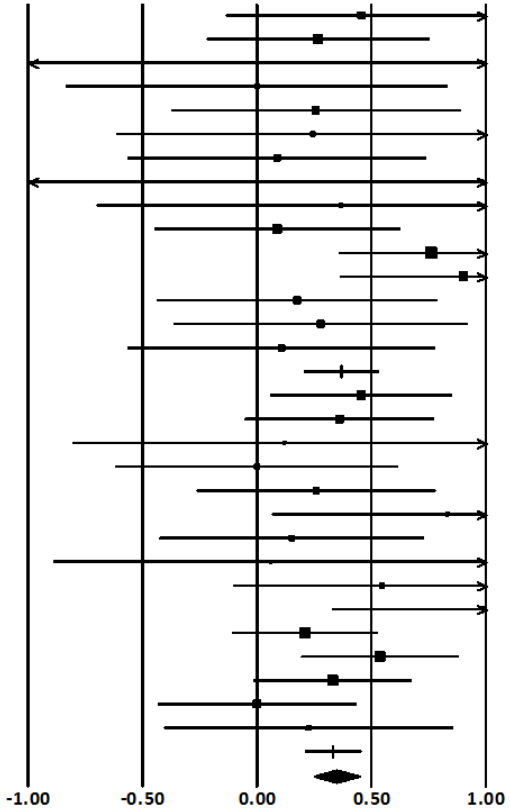
Hedges's g and 95% CI



Supplementary Figure 1b.

LAgFA Females and Males

Group by Sex	Study Name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	p-Value	Z-Value
Female	ASRB1-F	0.457	0.303	0.092	-0.137	1.050	0.132	1.507
Female	ASRB2-F	0.267	0.248	0.062	-0.220	0.754	0.282	1.076
Female	ASRB3-F	0.103	0.604	0.365	-1.081	1.287	0.864	0.171
Female	ASRB4-F	0.000	0.426	0.182	-0.836	0.836	1.000	0.000
Female	ASRB5-F	0.257	0.323	0.104	-0.376	0.890	0.426	0.796
Female	EDIN-F	0.245	0.440	0.194	-0.617	1.108	0.577	0.557
Female	Dublin-F	0.088	0.334	0.111	-0.566	0.742	0.791	0.264
Female	Galway-F	0.820	1.681	2.825	-2.475	4.114	0.626	0.488
Female	HUBIN-F	0.367	0.545	0.297	-0.701	1.436	0.500	0.674
Female	MCPR-F	0.089	0.275	0.076	-0.450	0.628	0.747	0.323
Female	TOP-F	0.761	0.207	0.043	0.355	1.168	0.000	3.675
Female	MCIC-F	0.902	0.275	0.076	0.362	1.441	0.001	3.276
Female	COBRE-F	0.175	0.314	0.098	-0.439	0.790	0.576	0.560
Female	Madrid-F	0.279	0.328	0.107	-0.363	0.922	0.394	0.852
Female	Oxford-F	0.108	0.344	0.118	-0.566	0.781	0.754	0.314
Female		0.368	0.084	0.007	0.203	0.534	0.000	4.367
Male	ASRB1-M	0.456	0.203	0.041	0.058	0.855	0.025	2.245
Male	ASRB2-M	0.361	0.212	0.045	-0.055	0.776	0.089	1.703
Male	ASRB3-M	0.121	0.472	0.223	-0.805	1.047	0.798	0.257
Male	ASRB4-M	0.000	0.316	0.100	-0.620	0.620	1.000	0.000
Male	ASRB5-M	0.259	0.267	0.071	-0.265	0.783	0.333	0.969
Male	EDIN-M	0.832	0.392	0.153	0.065	1.599	0.034	2.125
Male	Dublin-M	0.152	0.296	0.087	-0.428	0.732	0.607	0.514
Male	Galway-M	0.061	0.485	0.236	-0.890	1.013	0.899	0.126
Male	HUBIN-M	0.546	0.333	0.111	-0.106	1.198	0.101	1.640
Male	MCPR-M	0.994	0.339	0.115	0.330	1.658	0.003	2.934
Male	TOP-M	0.210	0.163	0.027	-0.110	0.530	0.198	1.288
Male	MCIC-M	0.538	0.176	0.031	0.192	0.884	0.002	3.049
Male	COBRE-M	0.331	0.177	0.031	-0.017	0.678	0.062	1.866
Male	Madrid-M	0.000	0.222	0.049	-0.436	0.436	1.000	0.000
Male	Oxford-M	0.225	0.322	0.104	-0.407	0.857	0.485	0.698
Male		0.333	0.064	0.004	0.209	0.458	0.000	5.233
Overall		0.346	0.051	0.003	0.247	0.446	0.000	6.808



White matter tract PCA loading for each site, across site mean, standard deviation and % coefficient of

		ASRB-1	ASRB-2	ASRB-3	ASRB-4	ASRB-5	EDIN	Dublin
Full Sample	CR	0.94	0.93	0.90	0.96	0.90	0.93	0.92
	CC	0.92	0.91	0.91	0.94	0.86	0.85	0.80
	ACR	0.86	0.85	0.86	0.86	0.84	0.80	0.85
	GCC	0.85	0.87	0.81	0.91	0.85	0.85	0.80
	IC	0.81	0.84	0.85	0.85	0.80	0.84	0.79
	PCR	0.86	0.80	0.80	0.88	0.78	0.86	0.75
	EC	0.83	0.77	0.83	0.79	0.80	0.81	0.71
	SLF	0.78	0.79	0.81	0.77	0.64	0.76	0.80
	BCC	0.85	0.77	0.84	0.85	0.71	0.71	0.72
	ALIC	0.77	0.78	0.84	0.70	0.66	0.77	0.74
	PTR	0.82	0.80	0.83	0.66	0.80	0.79	0.64
	SCR	0.79	0.79	0.75	0.89	0.65	0.85	0.76
	SS	0.77	0.78	0.76	0.58	0.70	0.76	0.71
	SCC	0.81	0.78	0.76	0.78	0.75	0.77	0.53
	CGC	0.77	0.78	0.82	0.78	0.79	0.74	0.66
	SFO	0.71	0.64	0.75	0.64	0.57	0.72	0.65
	FXST	0.63	0.58	0.51	0.65	0.65	0.74	0.51
	UNC	0.52	0.41	0.49	0.56	0.43	0.62	0.36
	FX	0.62	0.52	0.63	0.56	0.62	0.50	0.41

		ASRB-1	ASRB-2	ASRB-3	ASRB-4	ASRB-5	EDIN	Dublin
HC	CR	0.93	0.93	0.92	0.96	0.90	0.95	0.92
	ACR	0.82	0.80	0.86	0.86	0.80	0.81	0.85
	PCR	0.83	0.85	0.79	0.92	0.79	0.87	0.74
	IC	0.69	0.84	0.82	0.80	0.90	0.84	0.81
	CC	0.84	0.90	0.93	0.94	0.85	0.86	0.75
	GCC	0.68	0.88	0.78	0.91	0.84	0.86	0.75
	EC	0.77	0.74	0.85	0.86	0.77	0.83	0.65
	PTR	0.75	0.80	0.74	0.72	0.72	0.81	0.63
	SLF	0.75	0.78	0.85	0.79	0.73	0.72	0.78
	ALIC	0.50	0.75	0.84	0.61	0.72	0.77	0.74
	SCR	0.70	0.83	0.82	0.91	0.65	0.88	0.76
	BCC	0.72	0.76	0.93	0.85	0.65	0.72	0.65
	SCC	0.64	0.76	0.80	0.72	0.76	0.84	0.53
	SS	0.60	0.72	0.68	0.52	0.62	0.76	0.64
	SFO	0.50	0.68	0.91	0.79	0.63	0.75	0.58
	CGC	0.73	0.75	0.84	0.76	0.68	0.72	0.66
	FXST	0.59	0.64	0.37	0.72	0.58	0.76	0.47
	UNC	0.45	0.55	0.35	0.78	0.47	0.59	0.27
	FX	0.59	0.40	0.78	0.69	0.57	0.46	0.33
	SS	0.94	0.92	0.88	0.96	0.89	0.90	0.92
	CGC	0.92	0.91	0.87	0.94	0.86	0.83	0.86
	FX	0.86	0.88	0.86	0.86	0.85	0.75	0.83
	PTR	0.87	0.76	0.77	0.86	0.78	0.83	0.75
	ALIC	0.88	0.87	0.82	0.92	0.85	0.84	0.86
	SCC	0.83	0.79	0.86	0.76	0.81	0.76	0.79
	SLF	0.82	0.86	0.88	0.89	0.74	0.84	0.83

	FXST	0.86	0.77	0.73	0.86	0.74	0.68	0.81
	ACR	0.80	0.83	0.81	0.66	0.72	0.74	0.82
Sz	UNC	0.80	0.81	0.81	0.75	0.61	0.77	0.75
	EC	0.83	0.81	0.89	0.68	0.82	0.74	0.62
	CC	0.80	0.76	0.71	0.87	0.64	0.83	0.76
	IC	0.74	0.61	0.61	0.59	0.54	0.66	0.75
	PCR	0.79	0.81	0.76	0.77	0.56	0.80	0.85
	GCC	0.84	0.80	0.68	0.83	0.74	0.70	0.54
	SFO	0.79	0.80	0.77	0.81	0.85	0.75	0.64
	SCR	0.64	0.52	0.64	0.60	0.68	0.71	0.55
	CR	0.54	0.28	0.53	0.45	0.42	0.64	0.51
	BCC	0.63	0.60	0.49	0.46	0.65	0.48	0.40

ANOVA Reults comparing white matter tract loading between healthy controls and patients with schizo

		Sum of Squ	df	Mean Squa	F	Sig.
ASRB_1	Between G	0.113	1	0.113	8.47	*0.006
	Within Gro	0.482	36	0.013		
	Total	0.595	37			
ASRB_2	Between G	0	1	0	0	0.996
	Within Gro	0.715	36	0.02		
	Total	0.715	37			
ASRB_3	Between G	0.007	1	0.007	0.317	0.577
	Within Gro	0.738	36	0.021		
	Total	0.745	37			
ASRB_4	Between G	0.01	1	0.01	0.559	0.46
	Within Gro	0.662	36	0.018		
	Total	0.673	37			
ASRB_5	Between G	0	1	0	0.031	0.86
	Within Gro	0.54	36	0.015		
	Total	0.541	37			
EDIN	Between G	0.008	1	0.008	0.697	0.409
	Within Gro	0.387	36	0.011		
	Total	0.395	37			
Dublin	Between G	0.047	1	0.047	1.958	0.17
	Within Gro	0.873	36	0.024		
	Total	0.92	37			
HUBIN	Between G	0.112	1	0.112	4.203	*0.048
	Within Gro	0.96	36	0.027		
	Total	1.072	37			
MCPR	Between G	0.002	1	0.002	0.403	0.529
	Within Gro	0.158	36	0.004		
	Total	0.159	37			
TOP	Between G	0.003	1	0.003	0.118	0.734
	Within Gro	1.016	36	0.028		
	Total	1.019	37			
MCIC	Between G	0.003	1	0.003	0.186	0.669
	Within Gro	0.628	36	0.017		
	Total	0.632	37			

COBRE	Between G	0.009	1	0.009	0.45	0.507
	Within Gro	0.708	36	0.02		
	Total	0.717	37			
Madrid	Between G	0	1	0	0	1
	Within Gro	1.223	36	0.034		
	Total	1.223	37			
Oxford	Between G	0.04	1	0.04	2.052	0.161
	Within Gro	0.707	36	0.02		
	Total	0.748	37			

*p value does not survive Bonferroni correction for multiple comparisons

variance

HUBIN	MCPR	TOP	MCIC	COBRE	Madrid	Oxford	**Average**	**SD**
0.90	0.94	0.86	0.94	0.90	0.92	0.92	0.92	0.03
0.80	0.92	0.83	0.94	0.83	0.87	0.88	0.88	0.05
0.80	0.90	0.76	0.89	0.85	0.82	0.88	0.84	0.04
0.80	0.88	0.73	0.91	0.78	0.72	0.85	0.83	0.06
0.76	0.85	0.76	0.92	0.84	0.84	0.82	0.83	0.04
0.81	0.87	0.78	0.80	0.80	0.83	0.84	0.82	0.04
0.71	0.84	0.69	0.86	0.70	0.82	0.83	0.78	0.06
0.82	0.86	0.78	0.94	0.86	0.55	0.83	0.78	0.09
0.60	0.84	0.72	0.87	0.78	0.81	0.76	0.77	0.08
0.67	0.83	0.68	0.91	0.82	0.78	0.81	0.77	0.07
0.81	0.83	0.65	0.86	0.75	0.70	0.73	0.76	0.07
0.63	0.80	0.61	0.68	0.73	0.83	0.79	0.75	0.08
0.83	0.85	0.71	0.87	0.81	0.69	0.61	0.75	0.09
0.70	0.85	0.61	0.91	0.58	0.78	0.80	0.74	0.10
0.65	0.88	0.63	0.86	0.72	0.51	0.69	0.73	0.10
0.65	0.78	0.65	0.79	0.70	0.73	0.73	0.69	0.06
0.52	0.74	0.40	0.81	0.53	0.58	0.59	0.60	0.11
0.57	0.71	0.41	0.73	0.58	0.38	0.61	0.53	0.12
0.24	0.81	0.19	0.46	0.40	0.51	0.44	0.49	0.16

HUBIN	MCPR	TOP	MCIC	COBRE	Madrid	Oxford	**Average**	**SD**
0.87	0.94	0.88	0.93	0.91	0.91	0.90	0.92	0.03
0.76	0.90	0.76	0.88	0.82	0.83	0.82	0.83	0.04
0.73	0.86	0.77	0.77	0.80	0.80	0.81	0.81	0.05
0.74	0.85	0.77	0.92	0.81	0.84	0.83	0.82	0.06
0.76	0.94	0.82	0.93	0.84	0.93	0.88	0.87	0.06
0.79	0.91	0.73	0.89	0.79	0.81	0.83	0.82	0.07
0.71	0.87	0.68	0.83	0.75	0.81	0.82	0.78	0.07
0.80	0.85	0.65	0.85	0.64	0.66	0.66	0.73	0.08
0.72	0.83	0.78	0.93	0.81	0.55	0.81	0.77	0.09
0.66	0.85	0.69	0.90	0.77	0.76	0.70	0.73	0.10
0.58	0.79	0.63	0.59	0.80	0.87	0.74	0.75	0.11
0.51	0.88	0.72	0.85	0.75	0.86	0.81	0.76	0.11
0.66	0.83	0.63	0.87	0.55	0.82	0.78	0.73	0.11
0.78	0.84	0.72	0.88	0.78	0.86	0.48	0.71	0.12
0.52	0.81	0.66	0.75	0.74	0.85	0.59	0.70	0.12
0.48	0.90	0.59	0.86	0.68	0.29	0.60	0.68	0.16
0.36	0.71	0.40	0.79	0.41	0.62	0.61	0.57	0.15
0.60	0.71	0.40	0.65	0.60	0.32	0.57	0.52	0.15
0.12	0.83	0.17	0.42	0.34	0.62	0.41	0.48	0.21
0.92	0.94	0.85	0.93	0.90	0.91	0.95	0.91	0.03
0.81	0.89	0.84	0.94	0.82	0.93	0.88	0.88	0.04
0.88	0.90	0.79	0.88	0.86	0.83	0.95	0.86	0.05
0.86	0.92	0.81	0.81	0.80	0.80	0.85	0.82	0.05
0.83	0.81	0.73	0.89	0.77	0.81	0.87	0.84	0.05
0.72	0.79	0.73	0.88	0.67	0.81	0.84	0.79	0.06
0.80	0.87	0.68	0.91	0.87	0.84	0.80	0.83	0.06

0.66	0.76	0.72	0.86	0.79	0.86	0.73	0.77	0.07
0.89	0.87	0.65	0.85	0.84	0.86	0.69	0.79	0.08
0.69	0.78	0.61	0.89	0.85	0.76	0.88	0.77	0.08
0.82	0.82	0.62	0.84	0.81	0.66	0.78	0.77	0.09
0.66	0.85	0.53	0.74	0.72	0.87	0.84	0.75	0.10
0.76	0.72	0.57	0.79	0.69	0.85	0.81	0.69	0.10
0.91	0.92	0.76	0.93	0.89	0.55	0.84	0.80	0.12
0.75	0.88	0.50	0.93	0.58	0.82	0.84	0.74	0.13
0.74	0.83	0.70	0.86	0.75	0.29	0.78	0.74	0.14
0.64	0.80	0.29	0.80	0.58	0.62	0.52	0.61	0.13
0.55	0.72	0.44	0.76	0.56	0.32	0.64	0.52	0.14
0.33	0.76	0.28	0.35	0.43	0.62	0.40	0.49	0.14

phrenia

CV-%

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CV-%

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